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A quinine a day keeps the leg cramps away?

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1 A double-blind, placebo-controlled, cross-over trial of quinine in leg cramps occurring at rest was conducted in 22 elderly cramp sufferers.
2 Despite demonstration of impaired quinine elimination in the elderly, prescription of the traditional dose of 300 mg quinine bisulphate at night failed to produce a significant ($P = 0.1$) reduction in the number or severity of cramps.
3 There was a significant relationship between serum quinine concentration and attenuation of cramps. However, the simple expedient of increasing the nightly dose of quinine may carry the concomitant risk of cinchonism.

Keywords quinine leg cramps elderly

Introduction

Leg cramps are a common complaint of elderly patients, particularly in those whose mobility is reduced by arthritis or Parkinson's disease. Many remedies for nocturnal cramps have been suggested; the more traditional include putting corks or potatoes in the bed. Placing a magnet under the bed, raising the foot of the bed, and sleeping with the feet dorsi-flexed rather than plantar-flexed have all been recommended. Correction of fluid and electrolyte imbalance may cure cramps, as may withdrawal of certain drugs including the calcium antagonist, nifedipine, the H_2-receptor antagonist, cimetidine, the β_2-adrenoceptor agonists salbutamol and terbutaline, the antipsychotic drug, lithium, and the opiates, morphine and diamorphine (Drugs & Therapeutics Bulletin, 1982).

Quinine is the most commonly prescribed drug for the treatment of rest cramps and efficacy has been claimed by Moss & Herrmann (1940), Gootnick (1943) and Jones & Castleden (1983). However, inadequacies in design, inappropriate handling of data or small patient numbers cast doubt on their conclusions. We have conducted a double-blind, placebo controlled, cross-over study of maintenance treatment with quinine bisulphate for leg cramps occurring at rest. An interim report has been communicated (Smith *et al.*, 1986); we now present the final analysis.

Methods

Forty-three out-patients, who had sought treatment for leg cramps occurring at rest from their general practitioner or hospital doctor, were referred with a view to participation in the study. They were asked to give informed consent to entry into the study, which had Ethics Committee approval. Cramps were defined as involuntary and painful contractions of voluntary muscles. Patients with known hypersensitivity to quinine, unstable medical condition, fluid and electrolyte imbalance, variation in other medication, plans to change abode within 8 weeks, or suffering from exercise or drug-induced cramps, were

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excluded. The design of the study was a 2 week run-in period during which the patient did not take quinine, followed by two, sequential, 3 week treatment periods. Patients were required to fill in a diary of frequency, severity and duration of cramps on each morning of run-in and treatment periods. Those who suffered fewer than two cramps per week, did not keep an adequate record of their cramps or had measurable levels of quinine in their blood during the run-in period, were dropped from the study. The remainder were allocated, using a table of random numbers, to receive an initial treatment with quinine or placebo followed by a cross-over to the alternative. At the end of each treatment period a questionnaire, designed to identify symptoms attributable to quinine toxicity and to elicit the patient's evaluation of the treatment, was completed.

Treatments were quinine bisulphate, 300 mg, at night, or an identical, sugar-coated placebo tablet (both supplied by courtesy of H. K. Norton & Co. Ltd. U.K.). Tablets were dispensed in calendar packs, surplus tablets being collected at the end of each treatment period. Blood samples were taken for measurement of serum quinine concentration at home visits on the mornings of the first and second day of each treatment and on the morning after the final day of the second treatment. The nightly dose was to be taken at 22.00 h, the blood samples at 09.00 h. In practice the time between tablet administration, as recalled by the patient on the following morning, and collection of the sample varied between 10 and 12 h. Drug concentrations were measured by fluorimetric assay (Cramer & Isaksson, 1963) and by an h.p.l.c. method based on that previously described for quinidine (Drayer *et al.*, 1977).

Both the number of cramps experienced and their severity were compared on the two treatments. Severity was assessed by a 'cramp index', the product of the scores for intensity and duration. Intensity was scored according to whether a cramp was classified by the patient as mild (1), moderate (2), or severe (3), and duration, according to whether the patient estimated its duration at less than 1 min (1), 1–10 min (2), 11–20 min (3), 21–60 min (4), or more than 60 min (5). Number of cramps and cramp index were analysed by standard methods for a two period cross-over trial (Hills & Armitage, 1979), involving comparison of the effects of active and placebo treatments, and of the sequence of these treatments (paired *t*-tests), and assessment of the significance of any treatment/sequence interaction (unpaired *t*-test). Power to detect a 50% change in number of cramps, or in cramp index, was calculated using the observed pooled standard deviation of the differences between treatments. Preferences for active drug or placebo were analysed, assuming their distribution to be binomial, by comparing the proportion of preferences for the drug with 0.5.

Results

Of the 43 patients who entered the run-in, 22 patients, six male and 16 females, mean (s.d.) age 74 (8) years, completed the study. Eight were receiving diuretic, but showed no evidence of fluid or electrolyte imbalance. None were receiving other drugs known to induce cramps. Of the 20 excluded from the study at the end of the run-in period, 16 had suffered fewer than two cramps/week, two had not kept an adequate record of their cramps in the diary, and two had measurable levels of quinine in their serum (4.7 $\mu g\ ml^{-1}$ in one 1.47 $\mu g\ ml^{-1}$ in the other). One patient dropped out during the placebo treatment: she failed to report a loss of tablets.

The total number of cramps suffered by each of the 22 patients on placebo and quinine treatments is shown in Figure 1 and Table 1. The mean difference between treatments and mean sequence effect (Table 2) were not significantly different from zero ($t = 1.71$, $P = 0.1$; $t = 1.60$, $P = 0.1$, respectively). There was no significant interaction between nature of treatment and the sequence thereof ($t = 0.54$, $P = 0.6$). Compliance with treatment was judged inadequate in five of the 22 patients (Table 1). The investigators failed to collect blood samples on one occasion during a treatment period in patients 5, 8 and 10. In patients 16 and 20, the serum quinine concentration 11 h after the first dose of quinine was extremely low (0.00 and 0.03 $\mu g\ ml^{-1}$, respectively). One patient returned a calendar pack containing tablets: patient 16 returned two quinine tablets. When these five patients were excluded, there was still no significant treatment difference ($t = 1.64$, $P = 0.1$), sequence effect ($t = 1.22$, $P = 0.2$) or interaction ($t = 0.33$, $P = 0.7$).

The cramp index data were analysed similarly (Tables 1 and 2). There was no significant treatment difference, sequence effect of interaction, either in the whole group ($t = 1.62$, $P = 0.1$; $t = 0.74$, $P = 0.5$; $t = 0.23$, $P = 0.8$, respectively), or in the seventeen patients with adequate evidence of compliance.

The power of the statistical test was calculated, taking reduction of the number or severity of cramps by at least a half to be the effect that would justify maintenance treatment with quinine. The chance of detecting an effect of this magnitude,

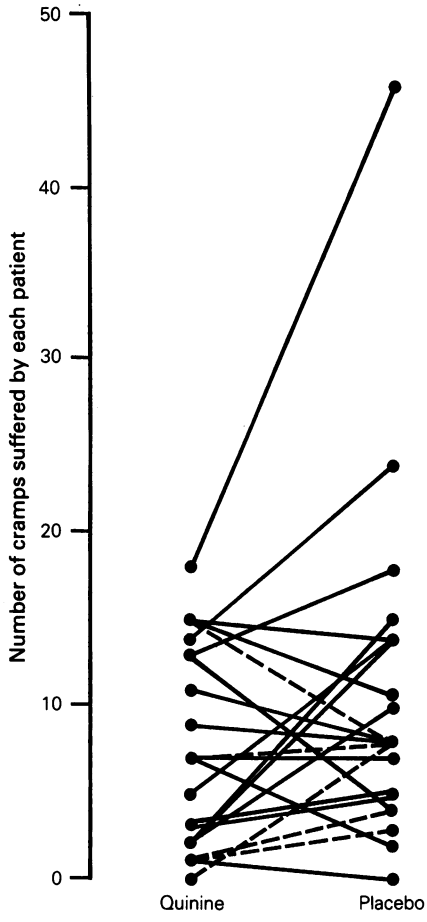

Figure 1 Total number of cramps experienced on quinine and placebo treatments by each of 22 patients. Data from five patients, in whom evidence of compliance was judged inadequate, are indicated by interrupted lines.

if it were present, was 75% in the case of the number of cramps and 70% in the case of the cramp index.

There was some evidence that the treatment differences detected in a given patient were dependent on the total number of cramps suffered and the magnitude of the cramp index, in that patient. Therefore the cross-over analysis was repeated using $\log_e$ (P+1/Q+1) data, where P is the number of cramps, or the cramp index, on placebo and Q is that on quinine. The conclusions were unaltered, the values for t calculated using transformed and original data being similar.

Thirty-three of the serum samples were assayed by both fluorimetric and h.p.l.c. methods: the difference (mean s.d.), −0.1 (0.4) μg ml^{-1}) between values for quinine concentration obtained by the two methods was not significant (paired t-test, $t = 0.26$, $P = 0.8$). Thus the fluorimetric method, with its double extraction technique, provided adequate separation of parent drug from its fluorescent metabolites. The values quoted here were obtained by this method, the coefficient of variation being 10% at a concentration of 2 μg ml^{-1} and 6% at a concentration of 1 μg ml^{-1}. Excluding the five patients with inadequate proof of compliance, the mean (s.d.) serum quinine concentration, 11 h after the first dose of quinine, 1.4 (0.5) μg ml^{-1} differed significantly from that 11 h after the last dose of quinine 2.3 (0.9) μg ml^{-1} (paired t-test, $t = 3.31$, $P = 0.003$). Accumulation of the drug was to be expected since the estimated half-time in seven of our elderly patients was 19 (4) h, mean ± (s.d.).

The relationship between the mean steady state quinine concentration attained and the difference in number and severity of cramps between placebo and active treatments was examined. Number of cramps and cramp index were skewed in distribution and were, therefore, log transformed as above. Figure 2 shows the relationship of the difference between treatments (log P+1/Q+1 data) with respect to both number of cramps and cramp index, and the log serum quinine concentration ($r = 0.60$, $P = 0.01$ and $r = 0.47$, $P = 0.06$, respectively).

Eight of the 17 patients shown in Figure 2 were receiving a diuretic: all had serum electrolyte concentrations within the reference ranges throughout. The difference in number and severity of cramps between placebo and quinine treatments was similar in those receiving and not receiving diuretics ($t = 1.4$, $P = 0.3$ (number of cramps); $t = 0.1$, $P = 0.9$ (cramp index).

The efficacy of quinine may vary according to the time which has elapsed after taking the dose. In Figure 3, we examine the distribution of number and severity of cramps, according to the hour of the day when they struck, during treatments with quinine and placebo. There appeared to be a small excess in the number of cramps occurring from 3–9 h after a nightly placebo tablet than in the same period after quinine. The severity of cramps suffered during these hours appeared to be independent of treatment. Ten hours and more after the dose had been taken, when the patients were carrying out their daytime activities, there were few cramps on either of the treatments.

In the 18 patients who completed the questionnaire, the preference with respect to the two

Table 1 Difference in number and severity of cramps between placebo and quinine treatments in 22 patients. Data from five patients, in whom there was judged to be inadequate proof of compliance, are shown in italics

Order of treatment	*Patient*	*Age (years)*	*Number of cramps*			*Cramp index*		
			Period 1	*Period 2*	*Difference**	*Period 1*	*Period 2*	*Difference**
	1	75	15	11	−4	75	54	−21
	3	63	13	4	−9	24	4	20
	4	74	1	0	−1	2	0	−2
	7	79	2	15	13	4	44	40
Quinine/	13	53	7	7	0	37	22	−15
Placebo	15	78	11	8	−3	39	31	−8
	17	79	14	24	10	43	141	98
	5	*78*	*15*	*8*	*−7*	*95*	*40*	*−55*
	10	*83*	*7*	*8*	*1*	*14*	*46*	*32*
	20	*83*	*1*	*3*	*2*	*1*	*44*	*43*
	2	65	14	2	12	85	8	77
	6	88	2	7	−5	10	59	−49
	9	77	18	13	5	42	31	11
	11	64	14	5	9	72	48	24
	12	74	8	9	−1	16	9	7
Placebo/	14	68	46	18	28	178	26	152
Quinine	18	72	5	3	2	18	6	12
	19	75	14	15	−1	101	125	−24
	21	73	5	3	2	21	18	3
	22	77	10	2	8	15	10	5
	8	*76*	*4*	*1*	*3*	*20*	*6*	*14*
	16	*86*	*8*	*0*	*8*	*63*	*0*	*63*

*Cramps on placebo treatment minus those on quinine.

Table 2 Mean treatment difference and sequence effect in 22 patients

	Number of cramps		*Cramp index*	
	Mean	*s.e.***	*Mean*	*s.e.***
Treatment difference*	3.1	1.8	16.9	10.4
Sequence effect*	−2.9	1.8	−7.7	10.4

*Treatment difference = ½ (A + B) and sequence effect = ½ (A–B); where A is the mean difference in cramps, placebo treatment minus active, in the group receiving quinine first, and B is the mean difference in cramps, placebo treatment minus active, in the group receiving placebo first.
**Pooled over all the data.

treatments was as follows: eleven preferred quinine, five placebo and two had no preference. The proportion preferring the active drug was not significantly different from 0.5 ($P = 0.2$) but the sample size is too small to draw definite conclusions about preferences. Symptoms attributable to quinine toxicity were not experienced by any of our patients.

Discussion

Our study illustrates the importance of re-evaluation of traditional remedies. A standard nightly dose of quinine (300 mg quinine bisulphate) had no statistically significant effect on number of cramps suffered by a group of elderly patients. It was acknowledged that the number

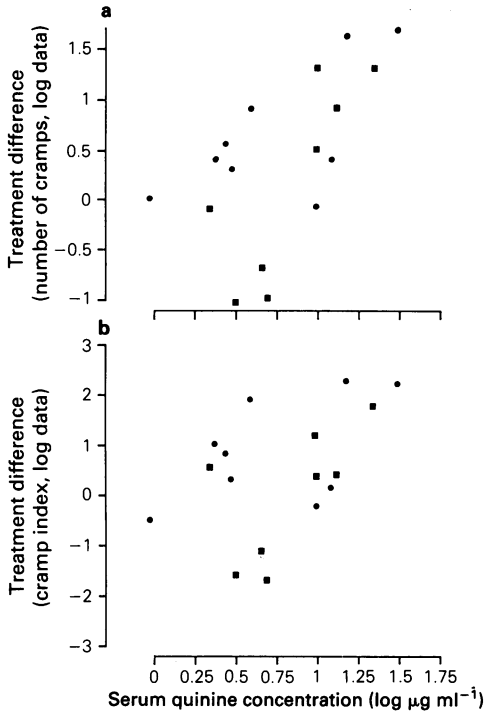

Figure 2 Relationship between the logarithm of the steady state serum quinine concentration and the difference between placebo and active treatment (log P+ 1/Q+1 data, as defined in Results) with respect to number and severity of cramps in 17 compliant patients. Patients receiving diuretics are represented by a square, those not receiving diuretics by a circle.

of cramps may be an inadequate measure of the suffering caused. However, we were unable to make a statistically significant distinction between placebo and quinine using a cramp index, which took into account the severity of the pain suffered and its duration, or the patients' stated preference with respect to the two treatments. The patient who suffered the most from cramps reported the greatest relief. Although patients with particularly frequent cramps might benefit from the standard dose, it would seem that little benefit accrues from its routine prescription. In the group as a whole fewer cramps were reported in the early morning on quinine than on placebo. Cramps were most frequent between 01.00 and 07.00 h, and, of course, the serum quinine concentration would still have been relatively high.

There was significant relationship between serum quinine concentration and attenuation of cramps in our group of patients, but further work is needed to define the optimal serum concentration. It may be that, if two sugar-coated tablets of quinine bisulphate a night could be tolerated, a significant effect on leg cramps would be observed. That is, there was an apparent need for a higher maintenance dose in our patients, despite their impaired elimination of quinine. The average elimination half-time was estimated at 19 h in seven of the patients. This is much longer than the half-time reported in previous small studies in younger volunteers (9 h in the study of Berlin *et al.* (1975): 6 h in that of Salem *et al.* (1978) and in elderly patients, who were relatively 'drug free' by comparison with those in the present study (7 h, Salem *et al.* (1978)). Berlin *et al.* (1975) also demonstrated that the half-time was dose-dependent, reaching a mean value of 16 h with a six-fold dose increment. The problem of tailoring the dose to the individual becomes even greater when the various oral presentations are considered: Garnham *et al.* (1976) demonstrated that the bioavailability of quinine was dependent not only on the solubility of the salt selected, but also on whether or not the tablets were sugar-coated.

The most well known dose-related adverse effect of quinine is cinchonism, a syndrome consisting of tinnitus, hearing loss, vertigo and visual disturbances, accompanied by headache, nausea and diarrhoea (Martindale, 1982). The ceiling concentration above which the risk of cinchonism bcomes substantial and the effect of age on that ceiling are unknown. In a younger patient cinchonism may easily be ascribed to the quinine and serve as a warning to reduce the dose. There are many reasons for an elderly person to suffer from dizziness, so that the warning may go unheeded. Any episode of vertigo in an elderly person puts them at risk of falling. This may result in serious injuries, such as fractured neck of femur, and the morbidity and mortality attendant on confinement to bed and operation.

Quinine is widely prescribed: in the U.K., in 1982, there was 1.4 million G.P. prescriptions for quinine, presumably in the treatment of cramps. It is well known (Medication for the Elderly, 1984), that non-compliance, as well as adverse drug reactions and interactions, increase with the number of drugs which an individual is prescribed. Our elderly patients were receiving a mean of 3.5 drugs other than quinine, some of which were prescribed for life-threatening conditions. Simply asking patients to keep a diary of their cramps reduced the number of patients fulfilling our arbitrary criteria for treatment with quinine by over a quarter. This may reflect the fluctuating nature of the condition, but also, possibly, the use by patients of an easily described symptom to draw attention to difficulties which are not so easy to articulate. Trying simple

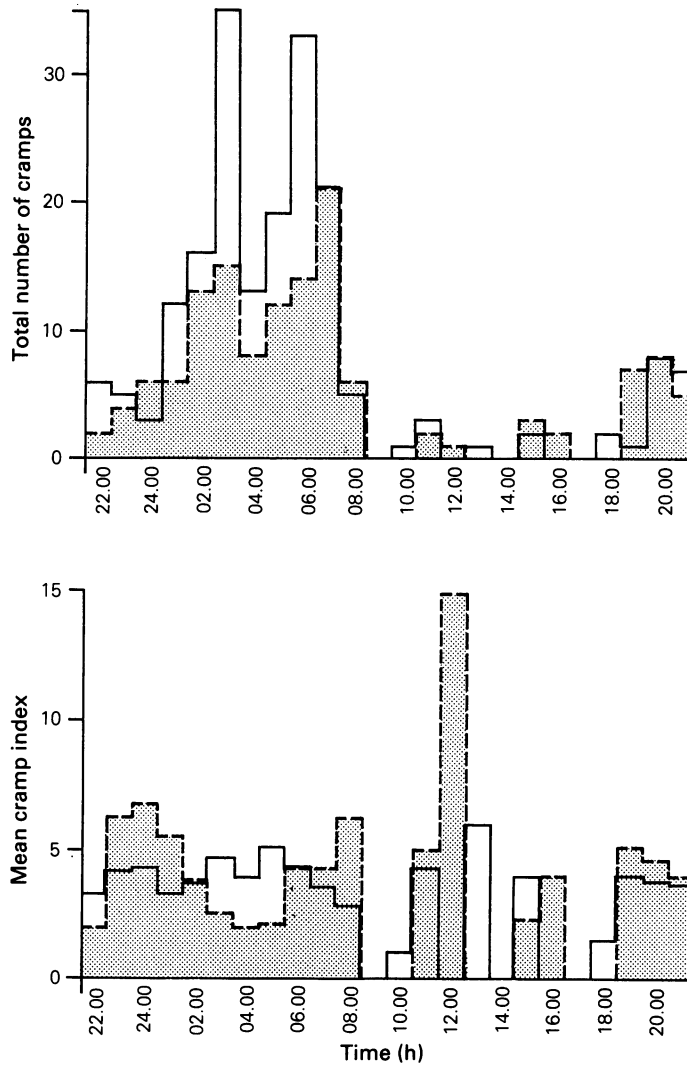

Figure 3 Total number of cramps experienced and their severity according to time of day during placebo (□) and quinine (▨) treatments. The data are from 17 patients; five of the 22 completing the study did not specify time of onset of cramp consistently in their diaries. The number of cramps occurring whilst the patients were involved in their day-time activities is small, explaining the erratic variation in the mean cramp index over this period.

physical measures, such as keeping the foot in a dorsiflexed position in bed and improving mobility, might save the patient from the risk of quinine toxicity and interference with more important treatment.

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